

雪旺氏细胞迁移在外周神经损伤修复中作用的研究进展

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[摘 要] 外周神经损伤 (PNI) 是常见的神经损伤疾病。作为神经髓鞘最主要的组成细胞, 雪旺氏细胞 (SCs) 在 PNI 后的修复中起重要作用。PNI 后, SCs 被激活, 并快速迁移至损伤部位, 与内皮细胞、细胞外基质 (ECM) 和成纤维细胞等组成连接远近残端的神经桥, 为轴突的形成提供通道, 引导轴突再生。SCs 向受损神经部位快速迁移能力大小是影响神经桥形成的关键因素。ECM、神经营养因子 (NT)、非编码 RNA [特别是长链非编码 RNA (lncRNA) 和微小 RNA (miRNA)] 及多种转录因子等, 通过多种信号转导途径, 参与 SCs 迁移能力的调控, 进而影响外周神经损伤后的修复, 但目前为止, 尚无关于影响 PNI 中 SCs 迁移能力因素及其作用机制的系统研究。现从 ECM、NT、非编码 RNA 和转录因子等方面系统综述 PNI 后影响 SCs 迁移能力的各种因素及其相关的信号转导通路, 为系统理解 SCs 在 PNI 修复中的作用提供依据, 为全面分析 PNI 后的修复机制提供参考。

[关键词] 雪旺氏细胞; 细胞迁移; 外周神经损伤; 修复; 微小 RNA; 长链非编码 RNA

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Research progress in role of migration of Schwann cells in repairment of peripheral nerve injury

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ABSTRACT Peripheral nerve injury (PNI) is a common neurological disorder. As the primary constituent cells of the myelin sheath, Schwann cells (SCs) play a crucial role in the repairment process after PNI. After PNI, the SCs are activated and rapidly migrate to the injury site, forming a neural bridge that connects the proximal and distal stumps in conjunction with the endothelial cells, the extracellular matrix (ECM), and the fibroblasts. This bridge provides a pathway for axonal regrowth and guides axonal regeneration. The ability of SCs to migrate quickly to the damaged nerve site is a key factor influencing the formation of the neural bridge. The ECM, NT, non-coding RNAs, particularly long non-coding RNAs (lncRNA) and microRNA (miRNA), and various transcription factors regulate the migratory capacity of the SCs through multiple signaling pathways, thereby affecting the repair of PNI. However, to date, there

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has been no systematic study on the factors influencing the migration of SCs in PNI or their underlying mechanisms. This article comprehensively reviews the various factors affecting the migration of SCs after PNI, including the ECM, NT, non-coding RNAs, and transcription factors, as well as the related signaling pathways. It aims to provide the basis for systematically understanding the role of SCs in PNI repairment and to offer the reference for comprehensive analysis of the repairment mechanisms after PNI.

KEYWORDS Schwann cells; Cell migration; Peripheral nerve injury; Repairment; MicroRNA; Long non-coding RNA

外周神经损伤(peripheral nerve injury, PNI)是神经损伤常见类型,通常由外伤、疾病或自身免疫反应引起,其临床病理表现为神经结构的破坏和功能障碍甚至丧失^[1]。雪旺氏细胞(Schwann cells, SCs)作为外周神经系统(peripheral nervous system, PNS)的主要细胞类型,在PNI后的修复过程中起重要作用,SCs占PNS细胞总数的70%~80%,是神经轴突外被层——神经髓鞘的主要组成成分,参与轴突的保护及神经冲动传递。周围神经遭受损伤后,SCs会经历表型转变并被激活,分泌大量细胞因子吸引并激活巨噬细胞,清除轴突和髓鞘碎片,激活的SCs还表现出较高的迁移能力,促进受损神经远端和近端的SCs迅速向对方迁移并汇合,形成关键的神经桥,引导轴突的生成,在神经损伤后的修复过程中发挥重要作用。近端SCs迁移还与近端残端组织相互作用,共同促进神经突触的生长^[1]。研究^[2]显示:PNI后糖蛋白非转移性黑色素瘤蛋白B(glycoprotein non-metastatic melanoma protein B, GPNMB)的表达上调,促进SCs迁移。虽然敲除SCs中CD146蛋白会降低细胞的活性和增殖能力,但却能够促进其迁移^[3]。

PNI修复中,SCs行为受多种因素调控,如细胞外基质(extracellular matrix, ECM)^[4]、微小RNA(microRNA, miRNA)^[5]、长链非编码RNA(long non-coding RNA, lncRNA)^[6]和神经营养因子(neurotrophin, NT)^[7]等,目前研究主要集中于探讨该类分子如何通过调控SCs增殖和髓鞘化等过程,进而在PNI后发挥促进修复作用,但对SCs在神经损伤后修复过程中迁移能力的影响及其机制的总结性报道较少,也缺乏对相关多信号通路和转录因子的系统性总结。现对ECM、NT、miRNA和lncRNA以及各转录因子对PNI后SCs迁移的影响及其机制进行综述,系统性揭示SCs迁移在PNI后神经修复中的作用。

1 SCs迁移在PNI修复中的作用

1.1 神经桥构建 在损伤神经中,修复型SCs与内皮细胞、ECM、成纤维细胞和血管组成连接远近残端的神经桥(也称为Büngner带),为轴突再生提供支架。在神经桥形成过程中,SCs受ECM调节改变形态,在组织桥上排列分布^[8]。在损伤后第2天,神经桥由巨噬细胞、中性粒细胞、成纤维细胞、内皮细胞和其他细胞类型组成,其中巨噬细胞和中性粒细胞数量最多,约占75%;第3天时,内皮细胞从远近两残端向神经桥中部大量涌入,占神经桥内细胞的20%,中性粒细胞百分率也略有升高,其他细胞百分率相应降低^[9-10]。第4天可观察到来自近端和远端神经残端的SCs向神经桥迁移,并在第7天汇合于神经桥内排列形成SCs索,而SCs索的建成是损伤后周围神经成功修复的关键^[9-10]。

1.2 促进轴突再生 SCs在引导再生轴突穿过神经桥到达远端神经残端方面起至关重要作用,如无SCs的引导作用,再生轴突则无法准确地向远端残端方向生长以再支配远端肌肉组织^[9, 11]。在受损神经近残端,SCs向远残端迁移的起始虽然晚于轴突再生,但从神经损伤后第5天开始,SCs的迁移速度却超过了轴突再生速度;在第6天,迁移的SCs会附着于再生轴突上,引导轴突穿过神经间隙,准确到达远端神经残端^[9, 11]。SCs还能提高轴突延伸的速度,CHEN等^[11]在小鼠模型研究中发现:如无SCs引导,随机延伸的轴突生长速度每天仅为85.7 μm ,且缺乏方向性;然而,在SCs作为延伸基质的情况下,轴突生长速度增加到每天433.1 μm ,与既往的研究^[12]结果一致。

2 影响SCs迁移的因素

2.1 ECM 在神经桥形成过程中,受损神经周围细胞分泌的ECM能明显改变SCs形态,使之变长并增强其迁移能力,进而更容易在神经桥中纵向排列而形成细胞索,促进受损神经修复。SCs体外培

养研究^[8]也证实ECM在调节SCs表型中起重要作用,不同组成的ECM可以诱导不同迁移速度的SCs亚型;重组人源性胶原蛋白Ⅲ(recombinant humanized collagen Ⅲ, rhCol Ⅲ)作为一种重要ECM成分,可增强SCs黏附、扩散和迁移能力。当暴露于rhCol Ⅲ型时,SCs中的神经生长因子及脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)的表达均明显升高,而上述因子被证实可增强SCs的迁移能力^[13]。SCs与ECM之间黏附的过程中,纤维连接蛋白(fibronectin, FN)是关键分子。体外模型实验研究^[14]表明:RSC96细胞中的Sox2因子直接控制RSC96中的FN表达和纤维生成,以介导其组织和轴突定向生长。研究^[15]表明:层黏连蛋白(laminin, LN)诱导SCs迁移的能力明显高于Ⅳ型胶原蛋白。因此SCs之间与黏附连接相关蛋白和SCs自身表达的性别决定区Y框2(sex determining region Y-box 2, Sox2)转录因子均可影响SCs迁移及Büngner形成^[14, 16]。周围神经中参与分泌组成ECM的成纤维细胞可分为感觉表型与运动表型,而不同表型的成纤维细胞可引导与之相同的感觉表型或运动表型SCs迁移。

2.2 NT 修复型SCs重编程后可上调包括神经生长因子(nerve growth factor, NGF)、BDNF、神经胶质细胞源性神经营养因子(glial-cell-line-derived neurotrophic factor, GDNF)和神经营养因子3(neurotrophin-3, NT-3)等在内的多种神经营养因子及神经生长因子受体(nerve growth factor receptor, NGFR)(也称p75NTR)^[17-18]的表达。而NGF和GDNF均能促进体外培养SCs的迁移和轴突生长^[19-21],但BDNF对于SCs迁移的影响尚存争议。MIN等^[9]研究显示:BDNF可增强SCs的髓鞘重塑能力,但对其迁移能力无影响。ADAM等^[20]研究显示:GDNF可促进SCs迁移,但对星形胶质细胞迁移无影响,BDNF可明显促进星形胶质细胞的活化和迁移却抑制SCs迁移。LIU等^[22]和LI等^[23]研究显示:大鼠SCs中BDNF表达神经受损后上调的部分miRNA被抑制,当BDNF被抑制后,SCs迁移能力相应降低。因此,BDNF对于SCs迁移的影响仍需进一步研究。

NGF和血管内皮生长因子(vascular endothelial growth factor, VEGF)可以诱导新生血管形成及神经再生,2种生长因子也可明显促进SCs迁移和轴

突伸长。LIU等^[19]研究显示:VEGF和NGF的混合物可促进SCs迁移。LI等^[21]将NGF和VEGF掺入猪脱细胞神经基质水凝胶(porcine decellularized nerve matrix hydrogel, pDNM-gel)中进行神经损伤治疗,结果发现:本身具有促进SCs迁移作用的PDNM-gel中单加或混加VEGF和NGF,均可促SCs增殖及迁移,明显促进伤口愈合、神经电生理传递和运动功能恢复。TSUCHIMACHI等^[24]利用经皮低强度脉冲超声每日治疗下牙槽神经横断部位,可增加横断部位SCs中NT-3的表达,并能促进神经横断后面部皮肤感觉障碍的功能恢复

2.3 非编码RNA lncRNA在多种生物过程中发挥表观遗传、转录和转录后调控作用。lncRNA可与miRNA结合,形成竞争性内源RNA(competing endogenous RNA, ceRNA)网络,进而参与生理活动。

PNI引发的差异表达的lncRNA已被证明在神经修复中发挥重要作用。近期研究^[25-30]表明:上调SCs中lncRNA,如HOXD反义生长相关长链非编码RNA(HOXD antisense growth-associated long non-coding RNA, lncRNA-HAGLR)、浆细胞瘤变异易位1长链非编码RNA(plasmacytoma variant translocation 1, lncRNA-PVT1)、Sox2基因过表达转录本长链非编码RNA(Sox2 overlapping transcript, lncRNA-Sox2ot)、H19长链非编码RNA(H19, lncRNA-H19)、代谢相关长链非编码RNA1(metastasis-associated lung adenocarcinoma transcript 1, lncRNA-MALAT1)和BC088259长链非编码RNA(BC088259, lncRNA-BC088259)等,或者沉默母系表达基因3长链非编码RNA(maternally expressed gene 3, lncRNA-MEG3)和生长阻滞特异性转录本5(growth arrest-specific transcript 5, lncRNA-GAS5),均可促进SCs迁移^[31-32]。lncRNA-HAGLR通过上调miRNA-204表达促进CDK5R1蛋白表达^[25],进而促进SCs迁移,并上调BDNF及其相应受体表达,最终促进大鼠受损神经的恢复^[33]。lncRNA-BC088259可与波形蛋白相互作用正向调控SCs迁移^[30]。lncRNA-MALAT1、lncRNA-PVT1和lncRNA-Sox2ot在神经受损后的SCs中表达增强,分别竞争性结合并负向调控miR-129-5p、miR-214和miR-9表达而促进SCs的迁移^[26-27, 29]。大鼠坐骨神经受损后的

瓦勒变性期间, lncRNA-H19在SCs胞质中表达上调, 促进SCs迁移, 但却会干扰背根神经节轴突的生长, 使髓鞘较薄, FENG等^[28]推测这可能由于lncRNA-H19激活信号素6D所致。当沉默受损坐骨神经SCs中lncRNA-MEG3后, 抑癌基因PTEN表达被抑制, 磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)和蛋白激酶B(protein kinase B, AKT)的磷酸化促进受损伤神经SCs迁移及轴突生长^[31]。

除了可促进SCs迁移的miR-3099^[34]和抑制迁移的miR-1b、miR-497、miR-129-5p、miR-214及miR-9之外, miR-148b-3p、miR-29a-3p、miR-497、miR-328a-3p和miR-195-5p也可影响SCs的迁移行为。神经横断后, 近端残端的SCs中miR-148b-3p表达减少, ZHANG等^[35]发现: 抑制miR-148b-3p可促进SCs迁移。在受损伤的坐骨神经中miR-29a-3p、miR-497和miR-328a-3p表达上调^[23, 36-37], 进而抑制SCs迁移。miR-29a-3p通过负向调节外周髓鞘蛋白22(peripheral myelin protein 22, PMP22)来影响SCs活性^[36]。miR-497通过抑制BDNF表达来抑制SCs的迁移和生存能力, LI等^[23]发现: 天麻素可调控miR-497对BDNF的影响, 并抑制氧化应激而促进外周神经损伤的恢复。miR-328a-3p仅在PNI后第1天和第14天升高, 而第4~7天却无明显变化^[37]。miR-195-5p对SCs增殖和迁移的影响完全相反, 在坐骨神经受损伤后, SCs中miR-195-5p表达降低, 增强SCs的增殖能力却抑制其迁移, 而当miR-195-5p过表达时, 表型出现逆转^[38]。

3 调控SCs迁移的信号通路

3.1 细胞癌基因jun(cellular-Jun, c-Jun)信号通路

外周神经受损后, SCs中的c-Jun信号通路被迅速激活, 改变SCs中多种效应分子表达, 进而调节SCs的重编程, 明显增强SCs的迁移能力^[17, 39-40]。SCs中富含半胱氨酸蛋白61(cysteine-rich 61, Cyr61)和Semaphorin3E蛋白^[39, 41], 均可上调c-Jun表达, 促进SCs迁移。其中Cyr61主要通过 $\alpha v\beta 3$ 整合素而增强c-Jun的表达^[39], 而Semaphorin3E蛋白则通过神经纤维网蛋白1、神经丛蛋白D1和血管内皮生长因子受体2等途径, 依靠自分泌或旁分泌机制上调c-Jun活性^[41], 因此, 二者有望在促进PNI后的修复中发挥重要作用。WANG等^[42]研究显示: 坐骨神经修复过程中, 蛋白激酶C θ 表达下调但促进SCs迁移和增殖。

3.2 索尼克刺猬(Sonic hedgehog, SHH)信号通路

SHH是PNI后修复过程中的关键信号分子, 其表达水平在神经损伤后大幅度上调, 并激活SCs中c-Jun信号通路^[43], 从而实现对SCs迁移的调控。研究^[44]显示: PNI后早期SHH的表达增加, 激活胃抑制肽/胃抑制肽受体信号途径, 胃抑制肽可能通过蛋白激酶A(Protein kinase A, PKA)/雷帕霉素复合物2的机制靶标(mechanistic target of rapamycin complex 2, mTORC2)途径调节SCs的迁移和细胞索的形成, 进而促进神经修复; 而损伤后期SHH表达降低, 其是否受到胃抑制肽信号途径的负向反馈的调节, 仍需进一步研究。褪黑素是一种参与神经再生过程的重要分子^[45]。PAN等^[46]研究显示: 褪黑素通过SHH信号通路促进SCs的增殖和迁移, 皮下注射褪黑素可明显促进小鼠PNI修复进程。

3.3 哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)及其信号通路

mTOR可通过多种信号通路调控细胞生长和代谢等生理功能。PNI后, SCs中基质金属蛋白酶9(matrix metalloproteinase-9, MMP-9)表达上调, 激活SCs中mTOR, 引发SCs代谢重编程, 增强SCs活性并促进轴突生长, 进而加速神经损伤修复。MMP-9可加速SCs向受损部位迁移, 在神经损伤后4和7d, MMP-9实验组SCs迁移距离明显大于对照组^[47]。PI3K/AKT/mTOR信号通路是mTOR传递信号的主要通路, PNI后急性期内PI3K/AKT/mTOR信号通路被激活, 但在损伤后1周迅速降低到正常水平^[48]。TAKAKU等^[49]研究显示: 艾塞那肽对背根神经节神经元和大鼠SCs的有益作用被PI3K抑制剂消除, 验证了PI3K/AKT信号通路在SCs存活、迁移和髓鞘形成中发挥重要作用。PTEN可负向调节AKT/mTOR信号通路的活性, 脂肪来源于细胞外泌体中的miR-22-3p可间接激活AKT/mTOR信号通路, 增强SCs的迁移能力^[50]。

3.4 信号传导及转录激活因子(signal transduction and activator of transcription, STAT)及其相关通路

JAK-STAT通路不仅参与细胞增殖、分化、凋亡和免疫调节, 还与神经损伤后的修复密切相关^[51-52]。在去神经支配期间, 长期持续激活STAT3通路, 对于SCs自分泌生存信号和再生过程中修复表型的形成及维持均为必需。敲除

STAT3可导致轴突再生异常、修复型SCs的关键标志物无法持续表达以及远端残端分泌的GDNF和BDNF减少^[16]。

PAN等^[51]研究显示:利用exendin-4培养SCs后,细胞中JAK2、STAT2和STAT3的磷酸化水平增加,激活JAK/STAT信号通路,促进SCs迁移。Runt相关转录因子3可被DNA甲基转移酶1抑制。WU等^[53]发现:Runt相关转录因子3在损伤坐骨神经组织和SCs中的水平明显高于假手术组,并在第7天时最高,其过表达可激活JAK/STAT信号通路,促进SCs迁移并抑制其凋亡。ZENG等^[54]研究显示:肌源性干细胞外泌体能促进SCs迁移,可能是由于外泌体内含有的miR-214可抑制SCs中PTEN基因表达,进而激活JAK2/STAT3通路。

3.5 Wnt 信号通路 Wnt信号通路在受损外周神经中被激活,在SCs的分化迁移、轴突重塑和神经元再生中发挥重要作用^[19, 55]。 β -连环蛋白(β -catenin)是Wnt信号通路中的关键下游效应蛋白,可介导Wnt多种生理病理效应。当沉默SCs中的Celsr2基因后,Wnt/ β -catenin信号通路受到抑制,进而阻碍SCs的迁移^[55]。Wnt/ β -catenin信号通路还可能参与SCs外泌体对机械损伤后背根神经节的保护作用,而相关抑制剂不但能抑制外泌体的保护作用,同时还能抑制Wnt/ β -catenin通路下游蛋白的表达^[56]。

4 影响SCs迁移和神经修复的其他因子

FOS样抗原1(FOS-like antigen 1, FOSL1)在周围神经挤压损伤部位的SCs中高度表达,FOSL1直接结合于SCs中受体蛋白酪氨酸激酶B2的启动子,上调后者转录水平,从而正向调控SCs的迁移^[57]。人B细胞淋巴瘤因子11A(B-cell lymphoma/leukemia 11A, BCL11A)正向调控SCs的活性和迁移能力,其表达水平在受损周围神经的SCs中明显上调,并可能通过结合并激活核受体亚家族2组F成员2(nuclear receptor subfamily 2 group F member 2, Nr2f2)的启动子,促进其表达,从而调节SCs的迁移^[58]。在损伤后小鼠坐骨神经远端神经的SCs中,白血病抑制因子(leukemia inhibitory factor, LIF)和转录因子SS18样蛋白1表达上调^[59-60],但LIF负调节SCs迁移。抑制转录因子SS18样蛋白1则可促进SCs增殖但抑制其迁移^[60]。研究^[61]显示:小鼠坐骨神经损伤

后,其损伤部位远端的SCs高表达成纤维细胞生长因子5(fibroblast growth factor 5, FGF5),该因子虽然抑制细胞外调节蛋白激酶1/2(extracellular regulated protein kinases 1/2, ERK1/2)活性,但可通过上调N-钙黏蛋白(N-Cadherin)的表达,促进SCs的迁移和黏附。CHEN等^[62]研究显示:生长因子双调节蛋白(amphiregulin, AREG)是一种重要的NT,SCs可通过合成该蛋白,促进神经突的生长和受损轴突的伸长,并激活ERK1/2,刺激SCs迁移并形成细胞束。

5 小结与展望

SCs迁移在整个修复过程中起重要作用,并具有极强的可塑性,如何提高SCs的迁移能力而促进轴突再生,对于促进PNI后修复和神经功能重建具有重要意义。目前,对SCs在神经修复过程中迁移作用的机制已有深入研究。这些研究主要集中在转录因子(c-Jun、Wnt和mTOR)以及STAT/JAK-STAT信号通路等,其在调控SCs迁移中起关键作用。损伤周围细胞所构成的微环境和表观遗传因素,如非编码RNA,也对SCs的迁移能力产生明显影响。激活或抑制上述分子及其信号通路,对提高SCs迁移能力和加速神经损伤的修复过程具有重要意义。进一步探索上述分子和信号通路在神经修复中的具体作用,以及其在不同修复环境下的作用机制,对于深化对外周神经损伤修复分子机制的理解以及开发基于调节SCs迁移的新治疗策略具有重要意义。运动康复方法,如游泳和跑步机训练,已被证实对于促进PNI后的轴突和肌肉修复具有积极作用^[63-65]。在动物模型中,早期介入游泳运动相比于晚期介入,能够带来更佳的恢复效果^[63]。轴突损伤后的4~7 d是SCs迁移的关键时期。跑步机训练能够通过提高受损坐骨神经中SCs的磷酸化ERK1/2蛋白水平,促进轴突再生^[64]。ERK1/2激活不仅对轴突再生至关重要,还能刺激SCs迁移,进而形成细胞束,对于神经修复过程极为重要^[62]。尽管运动疗法对SCs迁移的潜在影响值得关注,但目前直接相关的研究报道较少。未来的研究应重点探索运动疗法如何影响SCs的迁移和神经再生的具体机制,有助于优化运动康复方案,进一步提高PNI的治疗效果。

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